Prefrontal cortex glutamate and extraversion

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Extraversion is considered one of the core traits of personality. Low extraversion has been associated with increased vulnerability to affective and anxiety disorders. Brain imaging studies have linked extraversion, approach behaviour and the production of positive emotional states to the dorsolateral prefrontal cortex (DLPFC) and glutamatergic neurotransmission. However, the relationship between extraversion and glutamate in the DLPFC has not been investigated so far. In order to address this issue, absolute glutamate concentrations in the DLPFC and the visual cortex as a control region were measured by 3-Tesla proton magnetic resonance spectroscopy (1H-MRS) in 29 subjects with high and low extraversion. We found increased glutamate levels in the DLPFC of introverts as compared with extraverts. The increased glutamate concentration was specific for the DLPFC and negatively associated with state anxiety. Although preliminary, results indicate altered top-down control of DLPFC due to reduced glutamate concentration as a function of extraversion. Glutamate measurement with 1H-MRS may facilitate the understanding of biological underpinnings of personality traits and psychiatric diseases associated with dysfunctions in approach behaviour and the production of positive emotional states.

INTRODUCTION

The neuronal signatures of individual differences in human personality traits are of growing interest for neuropsychological and psychiatric research. Personality refers to an integrated pattern of thinking, feeling and behaving that varies among individuals but is stable within each individual over time (Sugiura *et al.*, 2000). According to the five-factor model (FFM) of personality, the dominant model of normal personality (Livesley, 2001), all phenotypical variation present in overt behaviour can be explained by five higher order factors comprising extraversion, neuroticism, openness, agreeableness and conscientiousness (Goldberg, 1992). Extraversion and neuroticism are the two core traits of personality that have achieved general acceptance, whereas the importance and definition of the other three factors are still being discussed (Depue and Lenzenweger, 2001). Individuals high on the extraversion dimension are often upbeat, optimistic, enjoy social contact, report more positive emotions in everyday life (McCrae and Costa, 2003) and show greater sensitivity to positive or rewarding stimuli (Lucas and Diener 2001; Banich *et al.*, 2009). Models that attempt to describe biological bases of personality propose lower prefrontal activity in extraverts compared to introverts reflecting less frontally based cognition, such as remembering events from the past, making plans for the future or problem

solving (Gray, 1972; Eysenck, 1986). Behavioural differences in extraverts therefore result from an innate drive to compensate for underactive reticulo-thalamo-cortical pathways (Eysenck, 1986) or lower activity in the behavioural inhibition system, a functional loop that includes the ascending reticular activating system, the frontal lobes, septal regions and the hippocampus (Gray, 1972). Accordingly, early neuroimaging studies that explored the neurobiological underpinnings of extraversion reported a decreased overall cerebral blood flow (Mathew *et al.*, 1984; Stenberg *et al.*, 1990) in extraverts. Johnson *et al.* (1999) specified these findings by showing that extraversion was correlated with enhanced blood flow in the anterior cingulate gyrus, right insular cortex and bilateral temporal lobes, but bilaterally decreased blood flow in the frontal lobe. Other brain regions that have been associated with extraversion in cerebral blood flow studies include the orbitofrontal cortex (Deckersbach *et al.*, 2006) and amygdala (Vaidya *et al.* 2007). Functional imaging studies that explored the neurobiological underpinnings of extraversion have found associations with activity in the amygdala, anterior cingulate cortex, dorsolateral and ventromedial prefrontal cortex and subcortical brain areas (Canli *et al.* 2001, 2002, 2004; Kumari *et al.* 2004; Simon *et al.* 2010; Brühl *et al.*, 2011). Structural studies showed a positive association between extraversion and grey matter concentration for the left amygdala (Omura *et al.*, 2005) as well as a thinner cortical grey matter ribbon in the lateral prefrontal cortex of extraverts (Wright *et al.*, 2006). These findings emphasize the role of the lateral prefrontal cortex

for extraversion. The dorsolateral prefrontal cortex (DLPFC) maintains widespread interconnections within the inhibitory top-down control network and is involved in the strategic implementation of control over one's thoughts and actions in line with specific goals or task-oriented behaviours (MacDonald *et al.*, 2000; Botvinick *et al.*, 2001). Several functional imaging studies have reported DLPFC activations during cognitive tasks that require response inhibition (Kelly *et al.*, 2004; Lavric *et al.*, 2004; Barber and Carter, 2005). Dysfunction of the DLPFC also appears to be a key feature of depression, and it has been suggested that dysfunction of the left DLPFC, in particular, may be related to deficits in the ability to experience positive affective states (Davidson *et al.*, 2003; Grimm *et al.*, 2008), which might explain why low trait levels of extraversion have been linked to increased vulnerability to affective and anxiety disorders (Watson and Clark, 1997; Kotov *et al.*, 2010). These disorders, which are marked by specific alterations in the production of positive emotional states and approach behaviour, seem to be associated with glutamatergic neurotransmission (Mathew *et al.*, 2008; Sanacora *et al.*, 2008; Walter *et al.*, 2009; Hashimoto *et al.*, 2010). Despite the links between personality traits and a predisposition towards psychiatric disorders as well as between specifically mood disorders and glutamatergic dysfunction, only few studies have attempted to investigate the role of glutamate for different personality traits. Gallinat *et al.* (2007) could show a negative association between anterior cingulate cortex (ACC) and hippocampal glutamate concentration and sensation seeking. Harm avoidance has also been reported to correlate negatively with glutamate concentration, but positively with GABA concentration in ACC (Kim *et al.*, 2009). Hoerst *et al.* (2010) investigated the association between glutamate levels in ACC with self-reported impulsivity in patients with borderline personality disorder as well as in healthy controls and found a positive correlation irrespective of diagnosis. Another MRS study by Montag *et al.* (2008) found a negative correlation between glutamate concentration in DLPFC and mental perspective taking. To the best of our knowledge, only one study has investigated the association between extraversion and neurotransmitter concentrations (Goto *et al.*, 2010) and reported a negative correlation with GABA in the frontal lobes. All these studies have been limited to correlations between neurotransmitters and personality traits, while no actual differences in neurotransmitter concentrations between subjects scoring high or low on extraversion or other personality dimensions have been reported. Furthermore, the relationship between extraversion and glutamate in the left DLPFC, a key region in the neural network subserving cognitive control, goal-directed behaviour and positive affective states (Davidson *et al.*, 2002), has not been investigated so far. This study aimed to investigate DLPFC glutamate concentration in introverts and extraverts, since several lines of evidence indicate a close relationship between DLPFC glutamate concentration and extraversion.

First, extraverts are psychologically characterized by an increased experience of positive emotions and high approach behaviour (McCrae and Costa, 2003). Secondly, extraverts are neurally characterized by a decreased bilateral cerebral blood flow (Mathew *et al.*, 1984; Stenberg *et al.*, 1990; Johnson *et al.*, 1999) and reduced lateral prefrontal grey matter (Wright *et al.*, 2006). Thirdly, low trait levels of extraversion have been linked to increased vulnerability to major depression and anxiety (Watson and Clark, 1997; Kotov *et al.*, 2010). Lastly, glutamatergic dysfunction has been reported in depression and anxiety disorders and these disorders are also characterized by specific alterations in the production of positive emotional states and approach behaviour (Mathew *et al.*, 2008; Sanacora *et al.*, 2008; Walter *et al.*, 2009; Hashimoto *et al.*, 2010). We hypothesized a lower DLPFC glutamate concentration in extraverts, based on models proposing lower prefrontal activity in extraverts (Gray, 1972; Eysenck, 1986) as well as on previous findings of decreased bilateral cerebral blood flow (Johnson *et al.*, 1999) and reduced gray matter in lateral prefrontal cortex of extraverts (Wright *et al.*, 2006). A further goal was to determine the regional specificity of the hypothesized differences in glutamate concentration between introverts and extraverts by investigating glutamate concentrations in a control region, i.e. the visual cortex (VC). We hypothesized a region-specific difference in DLPFC glutamate concentration.

MATERIAL AND METHODS
Subjects
The study was approved by the ethics committee of the Charité University Medicine (Berlin, Germany). Twenty-nine healthy female subjects (age 32.3 ± 13.3 years) were recruited through newspaper advertisements. All subjects gave written informed consent. Somatic as well as psychiatric health status was evaluated by a structured psychiatric interview (Mini-International Neuropsychiatric Interview) (Sheehan *et al.*, 1998) performed by a psychiatrist. No subject had to be excluded due to fulfilling the criteria for an axis I or axis II disorder according to DSM-IV criteria, diagnosed neurological and general medical disorders or clinically relevant abnormalities. Subjects were investigated with magnetic resonance spectroscopy, the NEO five-factor inventory (NEO- FFI, German version, Costa and McCrae, 1989; Borkenau and Ostendorf, 2008) and the State-Trait Anxiety Inventory (STAI; Laux et al., 1981). The NEO- FFI operationalizes the FFM of personality (McCrae and Costa, 1997) and provides domain scores that correspond to the five orthogonal factors extraversion, neuroticism, openness-to-experience, agreeableness and conscientiousness. It consists of 60 self-report items answered on a five-point Likert format. The personality traits are characterized as such (i) extraversion is characterized by talkativeness, assertiveness and energy. (ii) Neuroticism is characterized by upsetability and is the polar opposite of emotional stability.

(iii) Openness emphasizes originality, curiosity and ingenuity. (iv) Agreeableness is characterized by good-naturedness, cooperativeness and trust. (v) Conscientiousness is characterized by orderliness, responsibility and dependability. The five factors have been shown to be present in psychiatric as well as normative samples (Bagby and Ryder, 2000), and stability estimates for the domains and facets are substantial in both nonclinical (Costa and McCrae, 1992) and patient cohorts (Santor et al., 1997). In addition, evidence from twin studies indicates that each of the five broad trait domains have substantial and unique heritability coefficients (Jang et al., 1998).

The STAI is a self-report assessment device, which includes separate measures of state and trait anxiety. State anxiety reflects a transitory emotional state, may fluctuate over time and can vary in intensity. In contrast, trait anxiety refers to a general tendency to respond with anxiety to perceived threats in the environment.

MRS procedure

MRS was carried out on a 3-Tesla scanner (MEDSPEC 30/100, Bruker Biospin, Ettlingen, Germany). T1-weighted images were acquired using MDEFT [TE = 3.8 ms, TR = 20.53 ms; 128 contiguous slices, 1.5-mm thick; 1-mm in-plane $(x - y)$ resolution]. After localized shimming magnetic resonance spectra were recorded from voxels including the left DLFPC and the VC (Figure 1). The left DLPFC voxel

(Brodman areas 9, 10 and 46) extended $2 \times 2 \times 2$ cm and was positioned using coordinates as described by Rajkowska and Goldman Rakic (1995). The VC voxel extended $4 \times 2 \times 2$ cm and was positioned with the anterior border abutting the parietooccipital fissure and centred on the longitudinal fissure. Consistency between subjects was maintained by using the above-mentioned coordinates and anatomical landmarks for voxel placement on the set of sagittal and coronal 1H MR images. For metabolic fitting, spectra were acquired from equal voxels in spherical metabolite phantoms (0.1 mol/l metabolite, pH 7.2, 37°C). The point resolved spectroscopy (PRESS) sequence preceded by water suppression (3 Gauss chemical shift selective pulses of 25.6 ms duration) was used throughout. For one metabolite spectrum, eight subspectra of 16 phase cycled scans each were recorded with a repetition time of 3 s. The eight metabolite subspectra were corrected for eddy currents using water-unsuppressed spectra $(n = 8)$, automatically corrected for frequency and phase shifts, and added together to give 128 averages. Spectral quantification was carried out using a time domain–frequency domain fitting procedure (Schubert et al., 2004) that includes phantom basis spectra and prior knowledge and involves background estimation by regularization. In the present spectra, the amplitudes of total choline, total creatine, N-acetylaspartate (NAA), glutamate and glutamine resonances were fitted. Residual, minor contributions by macromolecules are accommodated in the baseline by the fitting procedure. Using an echo time of 80 ms, the applied methodology has
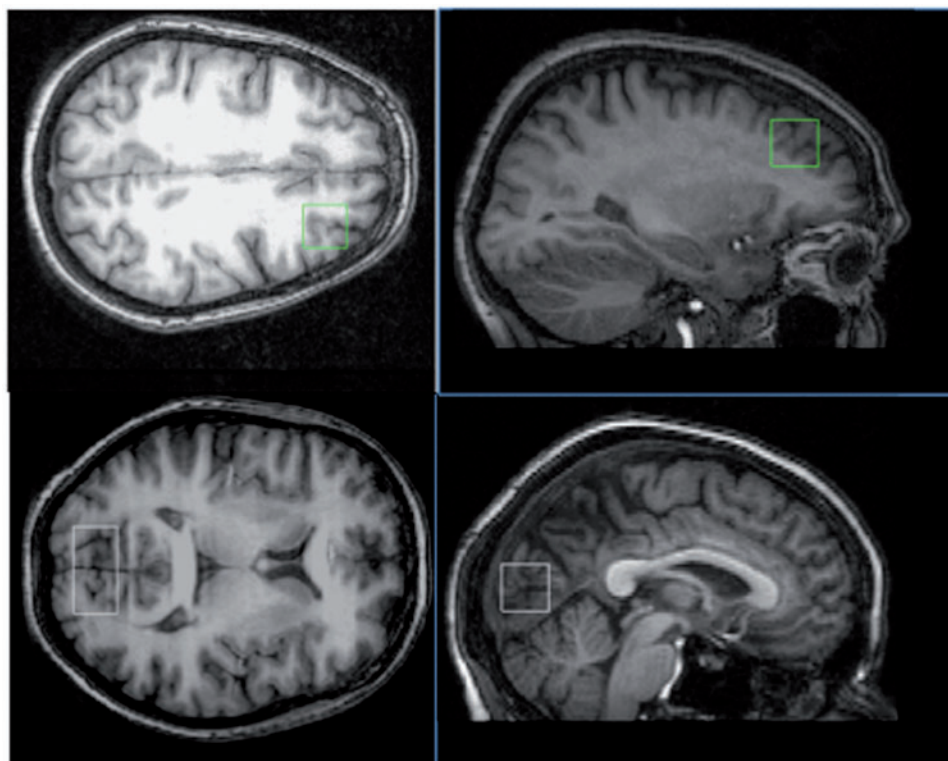
Fig. 1 Voxel positions shown on typical brain MDEFT images; upper panel: left dorsolateral prefrontal cortex; lower panel: visual cortex.

been shown to yield maximum selectivity for the glutamate C4 resonance over glutamine and gamma-aminobutyric acid (Schubert et al., 2004). Mean uncertainties [corresponding to Cramér–Rao lower bounds with added uncertainties from background modelling (Elster et al., 2005)] for the fitting of glutamate as small as 12.1% for the DLPFC voxel and 8.9% for the VC voxel were obtained. The fitted glutamate amplitudes were corrected for different coil loading by the phantoms and the individual subject's head (principle of reciprocity) and for relaxation effects using relaxation times measured previously (Schubert et al., 2004), assuming equal glutamate relaxation times in the investigated regions. Glutamate concentrations were corrected for the cerebrospinal fluid in the voxels studied by using the cerebrospinal fluid fractions obtained by segmenting the T1-weighted images with SPM2 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/spm2.html).

Statistical analyses

In this study, we focused on extraversion as the principal personality trait of interest. Median-split was used to create two groups of subjects with high, i.e. extraverts, and low, i.e. introverts, scores of extraversion on the NEO-FFI, respectively. To ensure the differentiation of the two groups, we confirmed our selection with normative data from a large German sample (Körner et al., 2008), which showed that subjects in our two groups scored indeed more than 1 s.d. above or below the average score for the normative group. Statistical calculations were carried out as indicated in the 'Results' section using SPSS for Windows (Release 16.0). Group differences were evaluated with t-tests for independent samples. Within- group comparisons were performed using paired t-tests. Correlation analysis was performed with Pearson correlation. All tests were performed at a level of significance equal to 0.05.

RESULTS

Extraverts had significantly lower glutamate concentration in the DLPFC than introverts ($P = 0.044$; Figure 2). In the extraverts, there were no differences in metabolite concentrations between the investigated brain regions. In the introverts, there was a trend for higher glutamate concentrations in DLPFC than in VC ($P = 0.054$; Figure 3). Concentrations of the other metabolites did not differ between introverts and extraverts. Correlations between metabolite concentrations and psychometric measures were performed separately for extraverts and introverts. In the introverts, glutamate concentration in DLPFC was associated with a lower state anxiety (STAI 1; $r = -0.59$, $P = 0.044$). There was no significant correlation between DLPFC glutamate concentration and state anxiety in the extraverts ($r = -0.18$, $P = 0.491$; Figure 4). The relationship between glutamate and anxiety was specific for the DLPFC. Glutamate concentration in VC
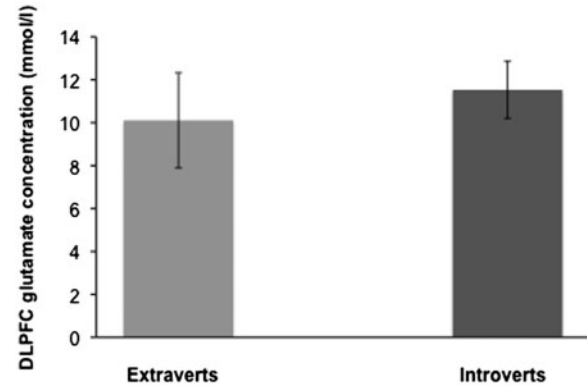
Fig. 2 Bar diagrams show DLPFC glutamate concentrations in extraverts and introverts. A significant difference between the two groups was observed ($P = 0.044$). DLPFC = dorsolateral prefrontal cortex.
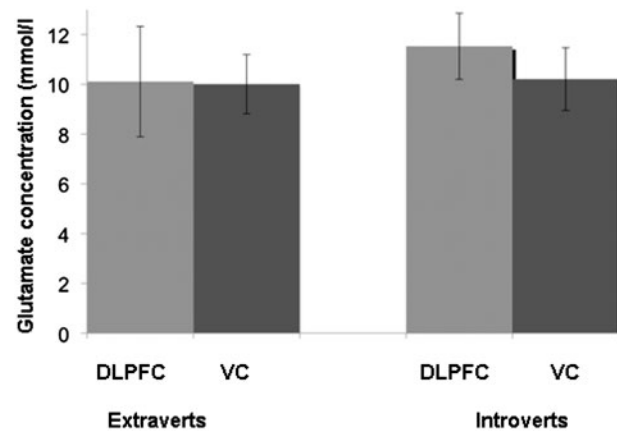

Fig. 3 Bar diagrams show glutamate concentrations in DLPFC and the control region (VC) in extraverts and introverts. A difference in glutamate concentration between the two regions was observed in introverts ($P = 0.054$), but not in extraverts. DLPFC = dorsolateral prefrontal cortex; VC = visual cortex.

was not associated with state anxiety in introverts ($r = 0.053$) or in extraverts ($r = -0.18$).

DISCUSSION

This study has three major findings: (i) introverts have significantly higher DLPFC glutamate concentration than extraverts; (ii) introverts have higher glutamate concentration in DLPFC than in VC and (iii) in introverts there is a negative association between DLPFC glutamate concentration and self-reported measures of state anxiety.

Previous studies have emphasized the role of the prefrontal cortex in extraversion and reported a decreased bilateral cerebral blood flow (Mathew et al., 1984; Stenberg et al., 1990; Johnson et al., 1999) as well as a relative regional thinning of the lateral prefrontal cortex (Wright et al., 2006). More medial regions of the frontal lobe, on the other hand, show a positive correlation with extraversion (Deckersbach et al., 2006; Simon et al. 2010; Brühl et al., 2011).
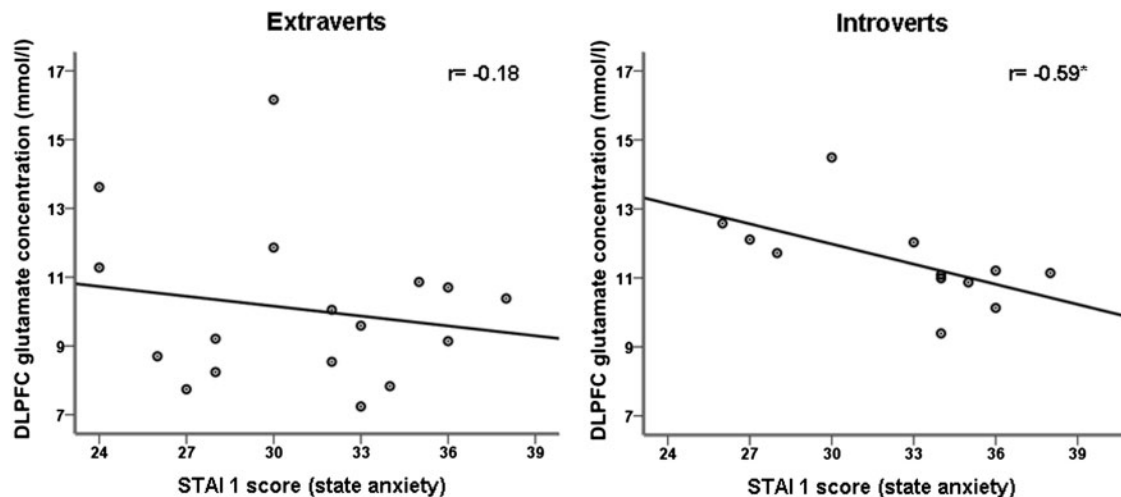
Fig. 4 Scatterplot of DLPFC glutamate concentrations and state anxiety (STAI 1) scores in extraverts and introverts. A significant negative correlation was observed in introverts, but not in extraverts. *$P < 0.005$.

Also, cerebral blood flow and activation in the amygdala in response to positive stimuli correlate with extraversion (Canli et al., 2002; Vaidya et al. 2007), and there is a positive association between extraversion and amygdala grey matter concentration (Omura et al., 2005). An association with extraversion has thus been shown for both cortical and subcortical regions suggesting that neural systems associated with this specific personality trait are not confined to higher level executive brain regions, but are rather represented at all levels of neural processing (Canli 2004). Since there seems to be a dissociation between lateral prefrontal, medial prefrontal and amygdala structural and functional findings in extraversion, one might assume a differential role for these regions. Our finding of decreased DLPFC glutamate in extraverts might be the result of reduced DLPFC gray matter concentration and/or decreased activation reported in previous studies (Johnson et al., 1999; Wright et al., 2006) and is consistent with two of the most significant biological models of personality, both of which hold that extraverts have lower cortical activity, especially in the frontal lobes (Gray, 1972; Eysenck, 1986). Lower activity and reduced glutamatergic neurotransmission in the DLPFC, a crucial region within the inhibitory topdown control network may be associated with reduced strategic implementation of control over thoughts and actions (MacDonald et al., 2000; Botvinick et al., 2001). A reduced topdown control of DLPFC on subcortical regions in conjunction with increased grey matter concentration in the amygdala in extraverts might also explain why amygdala activation to positive stimuli was found to correlate positively with the degree of extraversion in a previous study (Canli et al., 2002). Psychologically, these processes might be reflected in the behavioural characteristics of extraverts such as high approach and reward sensitivity and the propensity to experience a wide range of positive moods (McCrae and Costa, 2003). According to the above-mentioned biological

models of personality, higher DLPFC glutamate concentration in introverts due to higher activity in the behavioural inhibition system, namely the prefrontal cortex (Gray, 1972), reflects more engagement in cognitive processes, such as making plans for the future or problem solving (Gray, 1972; Eysenck, 1986). Unlike in extraverts, in the introverted subjects glutamate concentrations in DLPFC were higher than in the other cortical region investigated, i.e. the VC. This finding emphasizes the role of glutamatergic metabolism in the DLPFC as a key region for the implementation of cognitive control (MacDonald et al., 2000). Even though variation of Glx (glutamate + glutamine) across different brain regions has been reported, these differences concerned increases along the midline and between tissue types (Doelken et al., 2009) and can therefore not explain the differences in glutamate concentrations between cortical regions found in our study.

Previous MRS studies that investigated the role of glutamate for different personality traits focused mainly on the ACC, where a negative association between glutamate and sensation seeking (Gallinat et al., 2007) could be shown. In patients with borderline personality disorder as well as in healthy controls, a positive correlation with self-reported impulsivity has been reported (Hoerst et al., 2010). These differences in correlation patterns may be related to differences between these two personality traits. Even though impulsivity and sensation seeking are related constructs, current knowledge posits sensation seeking as one of several aspects of impulsivity (Meda et al., 2009). On the other hand, the dimension of extraversion is central to the sensation seeking personality trait (Zuckerman, 2007). Our finding of lower DLPFC glutamate concentration in extraverts therefore confirms the results reported by Gallinat et al. (2007). In animals the response to novelty, a construct which can be associated with approach behaviour and high sensation seeking (Dellu et al., 1992), has been extensively

investigated. Blockade of glutamate receptors such as the NMDA (*N*-methyl-*D*-aspartate)-receptor or AMPA (alphaamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-receptor has been found to increase novelty induced exploratory behaviour (Alvarez and Ruarte, 2001; Martínez *et al.*, 2002). In human studies glutamatergic dysfunction has been reported in psychiatric disorders marked by specific alterations in the production of positive emotional states and approach behaviour, such as depression or anxiety disorders (Mathew *et al.*, 2008; Sanacora *et al.*, 2008; Walter *et al.*, 2009; Hashimoto *et al.*, 2010). Not only have low trait levels of extraversion been linked to increased vulnerability to major depression and anxiety (Watson and Clark, 1997; Kotov *et al.*, 2010), but dysfunction of the DLPFC also appears to be a key feature of depression (Davidson *et al.*, 2003; Grimm *et al.*, 2008).

The finding of a negative association between DLPFC glutamate concentration and self-reported measures of state anxiety in introverts further confirms the hypothesized relationship between extraversion, DLPFC function and glutamatergic neurotransmission. Introverts show higher activity in regions of the behavioural inhibition system, such as the DLPFC (Gray, 1972), and have higher glutamate levels, which results in an increased top-down control of DLPFC on the amygdala as a critical structure in the fear network (Davis and Whalen, 2001). There might have been no association with trait anxiety due to the fact that an acute affective state is more strongly associated with extraversion (Gross and John, 1998). The relationship between DLPFC glutamate and state anxiety is specific for the DLPFC since there is no correlation with VC glutamate.

To our knowledge, only one study has investigated the association between extraversion and neurotransmitter concentrations (Goto *et al.*, 2010); and the authors reported a negative correlation with GABA/creatine ratios in the frontal lobes. In contrast to our examination, in this study the spectroscopic voxel was centred on the interhemispheric fissure.

There are several limitations to this study. The rather small sample size of this investigation has to be considered when interpreting the results. Furthermore, we confined the study to females within a limited age range since a previous study showed a significant age-related decline in glutamate in men (Chang *et al.*, 2009). Even though no gender differences have been reported for the extraversion dimension of the NEO-FFI (Chapman *et al.*, 2007), a replication of the results in a male sample is needed. Additionally, while we investigated a control region unrelated to extraversion, we cannot exclude lateralization effects due to the positioning of the DLPFC voxel in the left hemisphere. Several studies suggest that the left, but not the right DLPFC is specifically involved in approach-related positive affective states (Davidson and Irwin, 1999; Davidson *et al.*, 2002).

CONCLUSIONS

The present study indicates for the first time increased glutamate levels in the DLPFC of introverts as compared with extraverts. The increased glutamate concentration was specific for the DLPFC and negatively associated with state anxiety. The hypothesis of altered top-down control of DLPFC due to reduced glutamate concentration as a function of extraversion should be tested in further studies in healthy subjects as well as in psychiatric disorders marked by reduced approach behaviour.

Conflict of Interest
None declared.

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